Amendments to the Specification:

Please replace paragraph **[0030] with the following amended paragraph:**

[0030] Fig. 10: Lymphocyte Proliferation Assay on spleen cells from AN1792-treated (Fig. 10A)~~(upper panel)~~ or PBS-treated (Fig. 10B) ~~(lower panel)~~.

Please replace paragraph **[0035] with the following amended paragraph:**

[0035] Figs. 15~~(A-E)~~A-E: Aβ levels in the cortex of 12-month old PDAPP mice treated with AN1792 or AN1528 in combination with different adjuvants. The Aβ level for individual mice in each treatment group, and the median, mean, and p values for each treatment group are shown.

Please add the following five new paragraphs after paragraph **[0035]:**

Fig. 15A: The values for mice in the PBS-treated control group and the untreated control group.

Fig. 15B: The values for mice in the AN1528/alum and AN1528/MPL-treatment groups.

Fig. 15C: The values for mice in the AN1528/QS21 and AN1792/Freund's adjuvant treatment groups.

Fig. 15D: The values for mice in the AN1792/Thimerosol and AN1792/alum treatment groups.

Fig. 15E: The values for mice in the AN1792/MPL and AN1792/QS21 treatment groups.

Please replace paragraph **[0039] with the following amended paragraph:**

[0039] Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides ~~(SEQ ID NOS:37-77)~~ (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY ~~(SEQ ID NO:1)~~ (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

Please replace paragraph **[0040] with the following amended paragraph:**

[0040] Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides ~~(SEQ ID NOS:37-77)~~ (SEQ ID NOS:1-41) covering the complete AN1792 sequence. Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY ~~(SEQ ID NO:1)~~ (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

Please replace paragraph **[0068] with the following amended paragraph:**

[0068] H2N-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH ~~(SEQ ID NO:2)~~ (SEQ ID NO:42).

Please replace paragraph **[0075] with the following amended paragraph:**

[0075] In a further variation, an immunogenic peptide, such as a fragment of Aβ, can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include ~~Salmonella~~ *Salmonella* and ~~Shigella~~ *Shigella*. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with Aβ but nevertheless serve as mimetics of Aβ and induce a similar immune response. For example, any peptides and proteins forming β-pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to Aβ or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (see *Essential*

Immunology (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than Aβ peptides should induce an immunogenic response against one or more of the preferred segments of Aβ listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of Aβ.

Please replace paragraph **[0120] with the following amended paragraph:**

[0120] Some agents for inducing an immune response contain the appropriate epitope for inducing an immune response against amyloid deposits but are too small to be immunogenic. In this situation, a peptide immunogen can be linked to a suitable carrier to help elicit an immune response. Suitable carriers include serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, or a toxoid from other pathogenic bacteria, such as diphtheria, *E. coli,* cholera, or *H. pylori*, or an attenuated toxin derivative. Other carriers include T-cell epitopes that bind to multiple MHC alleles, e.g., at least 75% of all human MHC alleles. Such carriers are sometimes known in the art as "universal T-cell epitopes." Examples of universal T-cell epitopes include:

Influenza Hemagluttinin: $HA_{307-319}$ PKYVKQNTLKLAT ~~(SEQ ID NO:3)~~ (SEQ ID NO:43)

PADRE (common residues bolded) AKXVAAWTLKAAA ~~(SEQ ID NO:4)~~ (SEQ ID NO:44)

Malaria CS: T3 epitope EKKIAKMEKASSVFNV ~~(SEQ ID NO:5)~~ (SEQ ID NO:45)

Hepatitis B surface antigen: $HBsAg_{19-28}$ FFLLTRILTI ~~(SEQ ID NO:6)~~ (SEQ ID NO:46)

Heat Shock Protein 65: $hsp65_{153-171}$ DQSIGDLIAEAMDKVGNEG ~~(SEQ ID NO:7)~~ (SEQ ID NO:47)

bacille Calmette-Guerin QVHFQPLPPAVVKL ~~(SEQ ID NO:8)~~ (SEQ ID NO:48)

Tetanus toxoid: $TT_{830-844}$ QYIKANSKFIGITEL ~~(SEQ ID NO:9)~~ (SEQ ID NO:49)

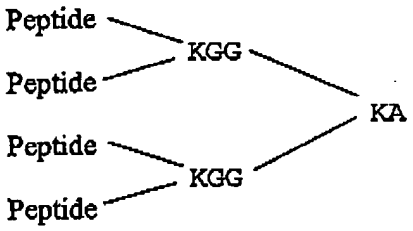
Tetanus toxoid: $TT_{947-967}$ FNNFTVSFWLRVPKVSASHLE ~~(SEQ ID NO:10)~~ (SEQ ID NO:50)

HIV gp120 T1: KQIINMWQEVGKAMYA ~~(SEQ ID NO:11)~~ (SEQ ID NO:51).

Please replace paragraph **[0127] with the following amended paragraph:**

[0127] The MAP4 configuration is shown below, where branched structures are produced by initiating peptide synthesis at both the N terminal and side chain amines of lysine. Depending

upon the number of times lysine is incorporated into the sequence and allowed to branch, the resulting structure will present multiple N termini. In this example, four identical N termini have been produced on the branched lysine-containing core. Such multiplicity greatly enhances the responsiveness of cognate B cells.



AN90549 (Aβ 1-7/Tetanus toxoid 830-844 in a MAP4 configuration):

DAEFRHDQYIKANSKFIGITEL ~~(SEQ ID NO:12)~~ (SEQ ID NO:52)

AN90550 (Aβ 1-7/Tetanus toxoid 947-967 in a MAP4 configuration):

DAEFRHDFNNFTVSFWLRVPKVSASHLE ~~(SEQ ID NO:13)~~ (SEQ ID NO:53)

AN90542 (Aβ 1-7/Tetanus toxoid 830-844 + 947-967 in a linear configuration):

DAEFRHDQYIKANSKFIGITELFNNFTVSFWLRVPKVSASHLE ~~(SEQ ID NO:14)~~ (SEQ ID NO:54)

AN90576: (Aβ 3-9)/Tetanus toxoid 830-844 in a MAP4 configuration):

EFRHDSGQYIKANSKFIGITEL ~~(SEQ ID NO:15)~~ (SEQ ID NO:55)

Please replace paragraph **[0128] with the following amended paragraph:**

[0128] Peptide described in US 5,736,142 (all in linear configurations):

AN90562 (Aβ 1-7/ peptide) AKXVAAWTLKAAADAEFRHD ~~(SEQ ID NO:16)~~ (SEQ ID NO:56)

AN90543 (Aβ1-7 x 3/ peptide): DAEFRHDDAEFRHDDAEFRHDAKXVAAWTLKAAA ~~(SEQ ID NO:17)~~ (SEQ ID NO:57)

Please replace paragraph **[0129] with the following amended paragraph:**

[0129] Other examples of fusion proteins (immunogenic epitope of Aβ bolded) include

AKXVAAWTLKAAA-**DAEFRHD-DAEFRHD-DAEFRHD**

~~(SEQ ID NO:18)~~ (SEQ ID NO:58)

DAEFRHD-AKXVAAWTLKAAA ~~(SEQ ID NO:19)~~ (SEQ ID NO:59)

DAEFRHD-ISQAVHAAHAEINEAGR ~~(SEQ ID NO:20)~~ (SEQ ID NO:60)

FRHDSGY-ISQAVHAAHAEINEAGR ~~(SEQ ID NO:21)~~ (SEQ ID NO:61)

EFRHDSG-ISQAVHAAHAEINEAGR ~~(SEQ ID NO:22)~~ (SEQ ID NO:62)

PKYVKQNTLKLAT-**DAEFRHD-DAEFRHD-DAEFRHD**

~~(SEQ ID NO:23)~~ (SEQ ID NO:63)

DAEFRHD-PKYVKQNTLKLAT-**DAEFRHD** ~~(SEQ ID NO:24)~~ (SEQ ID NO:64)

DAEFRHD-DAEFRHD-DAEFRHD-PKYVKQNTLKLAT

~~(SEQ ID NO:25)~~ (SEQ ID NO:65)

DAEFRHD-DAEFRHD-PKYVKQNTLKLAT

~~(SEQ ID NO:26)~~ (SEQ ID NO:66)

DAEFRHD-PKYVKQNTLKLAT-EKKIAKMEKASSVFNV-QYIKANSKFIGITEL-FNNFTVSFWLRVPKVSASHLE-**DAEFRHD**

~~(SEQ ID NO:27)~~ (SEQ ID NO:67)

DAEFRHD-DAEFRHD-DAEFRHD-QYIKANSKFIGITEL-FNNFTVSFWLRVPKVSASHLE

~~(SEQ ID NO:28)~~ (SEQ ID NO:68)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE

~~(SEQ ID NO:29)~~ (SEQ ID NO:69)

DAEFRHD-QYIKANSKFIGITELCFNNFTVSFWLRVPKVSASHLE-**DAEFRHD**

~~(SEQ ID NO:30)~~ (SEQ ID NO:70)

DAEFRHD-QYIKANSKFIGITEL ~~(SEQ ID NO:31)~~ (SEQ ID NO:77) on a 2 branched resin

peptide
Lys-Gly-Cys
peptide

EQVTNVGGAISQAVHAAHAEINEAGR ~~(SEQ ID NO:32)~~ (SEQ ID NO:71)
(Synuclein fusion protein in MAP-4 configuration)

Please replace paragraph **[0254] with the following amended paragraph:**

[0254] Preparation of coupled Aβ peptides: four human Aβ peptide conjugates (amino acid residues 1-5, 1-12, 13-28, and 33-42, each conjugated to sheep anti-mouse IgG) were prepared by coupling through an artificial cysteine added to the Aβ peptide using the crosslinking reagent sulfo-EMCS. The Aβ peptide derivatives were synthesized with the following final amino acid sequences. In each case, the location of the inserted cysteine residue is indicated by underlining. The Aβ13-28 peptide derivative also had two glycine residues added prior to the carboxyl terminal cysteine as indicated.

Aβ1-12 peptide	NH2-DAEFRHDSGYEVC-COOH (SEQ ID NO:33) (SEQ ID NO:72)
Aβ1-5 peptide	NH2-DAEFRC-COOH ~~(SEQ ID NO:34)~~ (SEQ ID NO:73)
Aβ33-42 peptide	NH2-C-amino-heptanoic acid-GLMVGGVVIA-COOH ~~(SEQ ID NO:35)~~ (SEQ ID NO:74)
Aβ13-28 peptide (SEQ ID NO:75)	Ac-NH-HHQKLVFFAEDVGSNKGGC-COOH ~~(SEQ ID NO:36)~~

Please replace paragraph **[0259] with the following amended paragraph:**

[0259] Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (βAPP) was constructed as described by Oltersdorf et

al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into ~~*E. coli*~~ *E. coli* and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please replace paragraph **[0317] with the following amended paragraph:**

[0317] To prepare formulation doses with alum (Groups 1 and 5), Aβ peptide in PBS was added to Alhydrogel (two percent aqueous aluminum hydroxide gel, Sargeant, Inc., Clifton, NJ) to reach concentrations of 100 μg Aβ peptide per ~~1 mg~~ 2 mg of alum. 10X PBS was added to a final dose volume of 200 μl in 1X PBS. The suspension was then gently mixed for approximately 4 hr at RT prior to injection.

Please replace paragraph **[0320] with the following amended paragraph:**

[0320] To prepare formulation doses with Freund's Adjuvant (Group 4), 100 μg of AN1792 in 200 μl PBS was emulsified 1:1 (vol:vol) with Complete Freund's Adjuvant (CFA) in a final volume of 400 μl for the first immunization. For subsequent immunizations, the antigen was similarly emulsified with Incomplete Freund's Adjuvant (IFA). For the formulations containing the adjuvants alum, MPL or QS-21, 100 μg per dose of AN1792 or AN1528 was combined with alum ~~(1 mg per dose)~~ (2 mg per dose) or MPL (50 μg per dose) or QS-21 (25 μg per dose) in a final volume of 200 μl PBS and delivered by subcutaneous inoculation on the back between the shoulder blades. For the group receiving FA, 100 μg of AN1792 was emulsified 1:1 (vol:vol) with Complete Freund's adjuvant (CFA) in a final volume of 400 μl and delivered intraperitoneally for the first immunization, followed by a boost of the same amount of immunogen in Incomplete Freund's adjuvant (IFA) for the subsequent five doses. For the group receiving AN1792 without adjuvant, 10 μg AN1792 was combined with 5 μg thimerosal in a final volume of 50 μl PBS and delivered subcutaneously. The ninth, control group received only 200 μl PBS delivered subcutaneously. Immunizations were given on a biweekly schedule for

the first three doses, then on a monthly schedule thereafter on days 0, 16, 28, 56, 85 and 112. Animals were bled six to seven days following each immunization starting after the second dose for the measurement of antibody titers. Animals were euthanized approximately one week after the final dose. Outcomes were measured by ELISA assay of Aβ and APP levels in brain and by immunohistochemical evaluation of the presence of amyloid plaques in brain sections. In addition, Aβ-specific antibody titers, and Aβ-dependent proliferative and cytokine responses were determined.

Please replace paragraph **[0322] with the following amended paragraph:**

[0322] The results of AN1792 or AN1592 treatment with various adjuvants, or thimerosal on cortical amyloid burden in 12-month old mice determined by ELISA are shown in Figs. 15A-15E. In PBS control PDAPP mice (Fig. 15A), the median level of total A in the cortex at 12 months was 1,817 ng/g. Notably reduced levels of A were observed in mice treated with AN1792 plus CFA/IFA (Fig 15C), AN1792 plus alum (Fig 15D), AN1792 plus MPL (Fig 15E) and QS21 plus AN1792 (Fig 15E). The reduction reached statistical significance ($p<0.05$) only for AN1792 plus CFA/IFA (Fig 15C). However, as shown in Examples I and III, the effects of immunization in reducing A levels become substantially greater in 15 month and 18 month old mice. Thus, it is expected that at least the AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 compositions will achieve statistical significance in treatment of older mice. By contrast, the AN1792 plus the preservative thimerosal (Fig 15D) showed a median level of A about the same as that in the PBS treated mice. Similar results were obtained when cortical levels of Aβ42 were compared. The median level of A42 in PBS controls was 1624 ng/g. Notably reduced median levels of 403, 1149, 620 and 714 were observed in the mice treated with AN1792 plus CFA/IFA, AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 respectively, with the reduction achieving statistical significance ($p=0.05$) for the AN1792 CFA/IFA treatment group. The median level in the AN1792 thimerosal treated mice was 1619 ng/g A42.

Please replace paragraph **[0390] with the following amended paragraph:**

[0390] The exact array of linear peptides recognized by the antibodies in the serum samples from animals immunized with AN1792 was determined by an ELISA that measured the binding of these antibodies to overlapping peptides that covered the entire Aβ1-42 sequence. Biotinylated peptides with partial sequences of AN1792 were obtained from Chiron Technologies as 10 amino acid peptides with an overlap of 9 residues and a step of one residue per peptide (synthesis No. 5366, No. 5331 and No. 5814). The first 32 peptides (from the eight amino acid position upstream of the N-terminal of AN1792 down to the twenty-fourth amino acid of AN1792) are biotinylated on the C-terminal with a linker of GGK. The last 10 peptides (repeating the thirty-second peptide from the previous series) are biotinylated on the N-terminal with a linker consisting of EGEG (SEQ ID NO:76)). The lyophilized biotinylated peptides were dissolved at a concentration of 5 mM in DMSO. These peptide stocks were diluted to 5 μM in TTBS (0.05% Tween 20, 25 mM Tris HCl, 137 mM NaCl, 5.1 mM KCl, pH=7.5). 100 μl aliquots of this 5 μM solution were added in duplicate to streptavidin pre-coated 96-well plates (Pierce). Plates were incubated for one hour at room temperature, then washed four times with TTBS. Serum samples were diluted in specimen diluent without azide to normalize titers, and 100 μl was added per well. These plates were incubated one hour at room temperature and then washed four times with TTBS. HRP-conjugated goat anti-human antibody (Jackson ImmunoResearch) was diluted 1:10,000 in specimen diluent without azide and 100 μl was added per well. The plates were again incubated and washed. To develop the color reaction, TMB (Pierce), was added at 100 μl per well and incubated for 15 min prior to the addition of 30 μl of 2 N H_2SO_4 to stop the reaction. The optical density was measured at 450 nm on a Vmax or Spectramax colorimetric plate reader.